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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,832	12/12/2001	Susan L. Kalled	A015/US CON2	1235

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,832	KALLED ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/8/04

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 1-24

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 12, 18-24

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1-11, 13-17

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse, filed 4/8/04, is acknowledged. Applicant's election of Group I and the species SLE in the reply filed on 4/8/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-11 and 13-17 are under consideration in the instant application, as the elected invention/species

Accordingly, claims 12 and 18-24 are withdrawn from consideration as being directed to a non-elected invention/species. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

2. The specification on page 1 should be amended to update that status of the priority applications claimed.

3. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Applicant is invited to clarify the numbering of the Experiments, as they appear to be out of order and missing certain numbers.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-11 and 16-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting certain immune responses with CD40L-specific antibody enables any "anti-CD40L compound" commensurate in scope with the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

First of all, applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies or enables any anti-CD40L compound other than CD40L-specific antibodies and soluble CD40 (see pages 6-8 of the Specification, Compounds).

It is not sufficient to define a specificity by an ill-defined functional property or ambiguous structural properties.

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Here, an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property (e.g. structural or functional of inhibiting CD40L interactions). Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed interrupter agents in a manner reasonably correlated with the scope of the claims broadly including any number of possible interrupter agents.

For example, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Therefore, structurally unrelated compounds encompassed by the claimed anti-CD40L compound would be expected to have greater differences in their activities.

However, applicant has not provided limited biochemical information for the particular claimed anti-CD40L compounds. Therefore, the problem of predicting protein structure from such limited information of anti-CD40L antibodies and soluble CD40 and, in turn, utilizing predicted structural determinations to ascertain functional aspects of an appropriate anti-CD40L compound and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Insufficient direction or guidance is provided to assist one skilled in the art in the selection of any other inhibitory ligands nor is there evidence provided that other certain anti-CD40L compounds or inhibitory ligands can inhibit immune responses associated with the costimulatory pathways associated with CD40L.

With respect to soluble CD40 (versus CD40L-specific antibodies); the following is noted.

Gray et al. (J. Exp. Med. 180: 141-155, 1994; 1449) teaches that the secondary response was not readily blocked by sCD40-γ1 treatment, indicating a relative independence of CD40 ligation of antigen-experienced B cells (see entire document, including Abstract). Here, if sCD40-γ1 were delayed until day 4 of the primary response, mice develop normal and possibly enhance memory responses.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, making and using the claimed anti-CD40L compounds would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

7. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Claim 15: It is apparent that the 5C8 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

Given the patented claims in Patent Nos. 5,474,771 (1449) and 5,993,816 (1449); the deposit of the 5C8 antibody/hybridoma under 35 USC 112, first paragraph is satisfied.

8. Claims 1-11 and 13-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-11 and 13-17 are indefinite in the recitation "wherein the anti-CD40L compound is an antibody or antibody fragment" to clearly recite that the specificity of the antibody and antibody fragments which bind CD40L (and additional functional properties) for clarity.

B) Claim 15 is indefinite in the recitation of "5C8" because its characteristics are not known. The use of "5C8" monoclonal antibody as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because "5C8" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct hybridomas / cell lines .

Applicant should amend the claim to include the recitation of ATCC No. HB 10916 (see page 4, paragraph 2) to obviate this rejection.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-11 and 13-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Black et al. (U.S. Patent No. 6,001,358; 1449) in view of Lederman et al. (U.S. Patent No. 5,993,816; 1449),

Black et al. teach the use of CD40L-/gp39-specific antibodies, including recombinant antibodies (columns 13-22) encompassed by the claimed methods to inhibit T cell-dependent antibody production in vivo, including those conditions mediated by autoantibody production (columns 31-32, overlapping paragraph), including SLE (column 1, paragraph 1; column 11, paragraph 2; column 33, line 58) (see entire document)

Black et al. teach the claimed methods are useful for the treatment or prevention of manifestations of autoimmune diseases (e.g. columns 33-34, overlapping paragraph), including that the determination of effective amounts would be determined by routine experimentation by the ordinary artisan at the time the invention was made (e.g. column 34, paragraph 1), in amounts sufficient to produce a therapeutic or prophylactic degree (column 34, paragraph 2) and which would vary upon the nature and severity of the condition being treated and invited undergoing treatment, column 34, paragraph 6).

Black et al. differ from the claimed methods by not disclosing the 5C8 CD40L-specific antibody and by not disclosing all of the dosing regimens.

Lederman et al. teach the use of CD40L-specific antibodies (e.g., column 7), including the 5C8 antibody (e.g. column 7, paragraph 6) to inhibit immunoglobulin production and B cell activation (see entire document, including column 11, Claims) and SLE (column 11, paragraph 5).

Lederman et al. teach that determining the effective amount was well known to those skilled in the art (column 11, paragraph 1).

Given inhibiting a chronic disease such as SLE in order to inhibit T cell dependent responses and B cell activation and immunoglobulin production, as taught by Black et al. and Lederman et al.; the ordinary artisan would have been determined the amounts and dosing of administering anti-CD40L antibodies to achieve a therapeutic or prophylactic effect depending on the nature of the manifestations of SLE in patients.

Therefore, it would have been expected that the claimed methods encompassing therapeutic intervals, including daily, weekly and month doses to prevent deterioration or to improve the patient's medical condition would have been met by administering anti-CD40L antibody to treat SLE patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to SLE by administering anti-CD40L antibodies at various intervals encompassing daily, weekly and monthly dosing to achieve prophylactic or therapeutic effects in a chronic disease such as SLE. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 1-11 and 13-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Black et al. (U.S. Patent No. 6,001,358; 1449) in view of Lederman et al. (U.S. Patent No. 5,993,816; 1449), as applied to claims 1-11 and 13-17 above and further in view of Mohan et al. (J. Immunol. 154: 1470-1480, 1995; 1449) and Early et al. (J. Immunol. 157: 3159-3164, 1996; 1449)

Black et al. and Lederman et al. are taught above.

Early et al. teach twice weekly injections of anti-CD40L antibody in an experimental murine lupus model from ages 4-10 months (see entire document, including Abstract, Results and Discussion). Early et al. Also teach that a brief treatment with three doses of anti-CD40L reduced the incidence of the development of severe nephritis in an experimental murine lupus model (page 3164, column 1).

Mohan et al. teach three injections of anti-CD40L antibody every other day in prenephritic lupus mice reduced the incidence of lupus nephritis up to 12 months of age (see entire document, including Abstract, Results and Discussion). Mohan et al. teach that the efficacy of the anti-CD40L antibody therapy would be beneficial in newly diagnosed lupus or in the early stages of disease flare-up (page 1479, column 1, paragraph 2).

Given inhibiting a chronic disease such as SLE in order to inhibit T cell dependent responses and B cell activation and immunoglobulin production, as taught by Black et al. and Lederman et al. And in further evidence of the experimental of short-term and long-term treatment of murine lupus models with anti-CD40L antibodies; the ordinary artisan would have been determined the amounts and dosing of administering anti-CD40L antibodies to achieve a therapeutic or prophylactic effect depending on the nature of the manifestations of SLE in patients.

Therefore, it would have been expected that the claimed methods encompassing therapeutic intervals, including daily, weekly and month doses to prevent deterioration or to improve the patient's medical condition would have been met by administering anti-CD40L antibody to treat SLE patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to SLE by administering anti-CD40L antibodies at various intervals encompassing daily, weekly and monthly dosing to achieve prophylactic or therapeutic effects in a chronic disease such as SLE. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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